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Objectives: To investigate neurophysiological parameters which possibly distinguish subtypes I and II of patients with a bipolar disorder, and contrast the findings with observations from a group of schizophrenic patients and a group of healthy controls.
Methods: Sixty-six volunteers underwent a MRI scan to determine the number and location of white matter lesions (WSL). A electrophysiological registration was made while all volunteers performed a auditory 'oddball' task, and the amplitude of the resulting P300 wave was compared.
Results: Earlier reports of higher numbers of WSL in bipolar disorder were not replicated in this study. Subtypes I and II showed a different P300 amplitude and subtype I resembled the results of the schizophrenia group.
Conclusion: Bipolar patients in remission have a functional brain disorder that is expressed by a change in physiological response to external stimuli.

Key words: bipolar disorder; P300; white matter lesions

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Introduction

The increasing availability and precision of neuroimaging techniques over the last few years have greatly facilitated the *in vivo* study of the relationship between anatomical anomalies and psychopathology. Anatomical imaging techniques such as single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI) or functional imaging such as event related potentials (ERP) or functional magnetic resonance imaging (fMRI) are now readily available as research tools. In a first MRI study with bipolar disease (BD) patients in 1985 (1) volumetric differences were found between the patient group and normal controls. Later studies with more refined techniques reported quantitative differences in individual structures and differentiation in white and grey matter (2). The use of different imaging techniques in many of the early studies makes their comparison difficult and could account partially for contradictory findings. Nevertheless, this imaging approach has played a crucial role in the discussion of the biological basis of affective disorders (3,4). According to mainstream models of affective disorders the prefrontal cortex plays a central role, interconnected to a number of specific subcortical structures: brain stem, thalamus, hypothalamus, basal ganglia and cerebellum (5). According to some studies the disrupted functionality is caused by lesions in pathways interconnecting these structures (6,7). This would be the case particularly in BD. In a majority of studies with BD patients white matter lesions (WML) were reported, especially in periventricular regions, the 'Bands', which could have a vascular origin (8).

Besides anatomical imaging there has been a long tradition of functional imaging research, both in unipolar depression (UD) and BD. Studies with ERP, relating behaviour with electrocortical activity measured on the scalp, have played a leading role. An often-used technique uses the P300 paradigm, which produces a positive-going electrical potential (wave) at about 300 milliseconds after presenting subjects with a novel stimulus. The

P300 can be considered as a measure of attention devoted to a stimulus and is part of the orientation response. In contrast to the vast literature concerning deviances in P300 parameters (amplitude, latency) in (sub)groups of schizophrenic patients, relatively little is known about P300 in affective disorders. In previous studies employing a visual P300 paradigm BD patients could be distinguished from UD patients on differences in latency (9) and amplitude (10) of the P300. A relationship has been proposed between smaller P300 amplitude and clinical exacerbations (11). In a large study investigating effects on P300 Muir et al. (12) compared a group of BD patients ($n = 79$) with a group of UD patients($n = 48$), schizophrenic patients ($n = 96$) and normal controls ($n = 213$). The major finding was a significant lengthening of P300 latency in the schizophrenic and BD groups compared to both the UD group and normal controls. The finding of a difference between the BD and UD groups has been replicated by Souza (13) and could point to a difference in neuro-anatomical organization of the disorder.

Recent clinical research on BD has focused on the difference between subtypes BD-I and BD-II (14,15). BD-II is a diagnostic category that can be distinguished from BD-I with respect to genetic (16), biological (17), clinical (18) and pharmacological (19) aspects and has a unique DSM-IV classification. In this study we looked for possible neurophysiological parameters that could distinguish these subtypes, notably white matter lesions in subcortical brain structures and differences in P300 parameters in an auditory oddball reaction time task. The results were further compared to those of a matched (age, gender) group of schizophrenic patients and normal controls tested previously at our institute (20). Based on clinical observations we hypothesize that the BD-I group will differ from the BD-II group and that the data of the former would resemble more closely that of the schizophrenic group, and data of the latter more closely the normal controls.

Methods

Subjects

A total of 66 subjects were included for the data analysis, divided into three different groups: the first group comprised 22 schizophrenic patients (12 male, 10 female), mean (SD) age 41.4 (6,7) years, mean (SD) BPRS score 46.2 (1,10), diagnosed according to DSM-IV criteria and verified through the Composite International Diagnostic Interview (CIDI) (21). The second group comprised 22 patients with a bipolar disorder (six male, 16 female), mean age (SD) 47.7 (3,8), mean (SD) HAM-D score 3.4 (3.0), mean (SD) YMRS score 0.8 (1,5), of whom 12 fulfillled the criteria for BD-I subtype and 10 for BD-subtype II. The diagnosis was verified by means of the Structured Interview for DSM-IV Disorders (SCID-IV) for BD patients (22). The last group comprised 22 healthy volunteers (10 male, 12 female), mean age (SD) 41.4 (3,11) years, without any present or past history of a psychiatric disease, verified by means of the CIDI. All BD patients were solicited from the Academic Hospital Maastricht (azM) and the Rumke group in Utrecht (Stanley Foundation Bipolar Network). The schizophrenic patients were recruited from ongoing research in the azM and the healthy controls through newspaper advertisements. All BD patients were in remission for at least 2 months at the time of inclusion (DSM-IV criteria for full remission) The mean (SD) number of depressive episodes was 6.2 (1,5) and mean (SD) number of manic or hypomanic episodes was 3.9 (3,5). A total of 16 patients in the BD group were taking lithium medication and six were taking carbamazepine. All patients in the schizophrenic group were out-patients and all but one were taking antipsychotic medication (mean (SD) chlorpromazine equivalent of 329 (214) mg). Exclusion criteria for all were age: above 60 years, left-handedness, any history of serious diseases or trauma accompanied by unconsiousness of more than 1 hour, other psychiatric conditions or the use of psychoactive compounds.

Apparatus

MRI imaging. All subjects were scanned on a Philips ACS-II 1.5 Tesla Gyroscan with a full brain scan using a slice thickness of 1.5 mm. All images were judged blind twice by the same experienced radiologist. Lesions were classified on a semiquantitative scale following the method described by van Achten et al. (23), in which lesions are described in eight different brain regions. Periventricular lesions were classified on a 1–3 scale and white matter lesions (WML) were classified as large, medium or small.

Erp-p300. A classic auditory 'oddball' paradigm was used to elicit a P300 ERP. All subjects were instructed to react by means of a button-press to target stimuli (2000Hz, 100 ms, 80dB) that were interspersed in a series of non-target stimuli (1000Hz, 100 ms, 80 dB). Interstimulus time was 1 s and targets and non-targets were presented in a random order with a chance of 15% and 85%, respectively. During each presentation an EEG recording was made, starting 100ms prior to

presentation and lasting 800 ms. Data of 22 measuring points were stored with 'linked ears' as a reference. Sample rate was 1000 Hz, with a frequency response between 0.15 Hz and 70 Hz (12 dB/oct). Eye movements (EOG) were recorded separately and trails with more than 50 μV EOG were rejected. Data collection lasted until 32 trials were collected without artefacts of each condition. All electrodes (AgAgCl, Bristol type) were placed according to the international 10/20 system with the following exceptions: TCP1 was placed at the junction of the diagonals formed by C3-T5 and P3-T3; CP1 was placed on the junction of the diagonals Cz-P3 and Pz-T3. On the contralateral side TCP2 and CP2 were placed in an analogue manner. Figure 1 shows an overview of the montage. All signals were registered with a Nihon-Kohden Neurofax EEG recorder. Data storage, averaging and experimental control were managed with the InstEP software system. All registrations were carried out in a sound and light attenuated room.

Statistical analyses

All analyses were carried out using the SPSS software package for Windows (version 9).

MRI data. The number and size of signal hyperintensities did not follow a normal distribution over groups and therefore analysis was carried out using non-parametric procedures (chi-square and Kruskal–Wallis). Correlations between P300 amplitude and signal hyperintensities were described by Spearman's rank order correlation coefficient.

ERP data. Parametric analysis of the P300 data was carried out on the difference between mean peak-to-peak amplitudes of target and nontarget conditions. First a MANOVA was performed to detect an overall difference between the three groups and subsequently the data of the BD group were compared with those of the control and schizophrenic groups. The subdivision in BD-I and BD-II was treated as a within-group factor. The level of significance for all analyses was set to: $\alpha = 0.05$

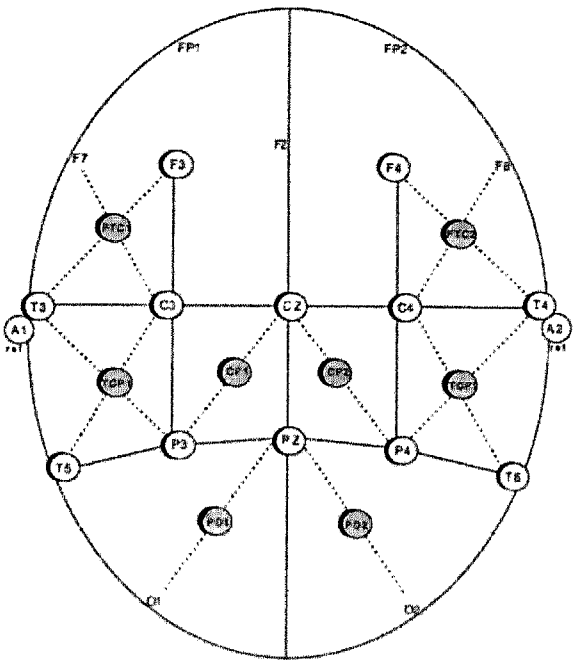

Fig. 1. The montage of electrodes on the head according to the 10/20 system with 'interpositions'.

Results

MRI

Small and medium-sized lesions were found in 18 of 22 BD patients, 13 of 22 schizophrenic patients and 10 of 22 controls. The differences are not significant with respect to number, size or type of lesion. Most lesions were found in frontal brain regions. The relatively high number of lesions in the normal group has not been found in previous studies.

ERP

Figure 2 shows the mean P300 amplitude for all groups at six measurement points at which differences were found between two or more groups. The corresponding P300 peak values are shown in shows the number and size of signal hyperintensities for all groups. Table 1. Previous research by our group had already shown a difference in P300 amplitude between the schizophrenic group and normal controls (20). MANOVA analysis shows significant differences between the three groups at

Table 1. Mean P300 peak amplitudes in microvolts for all groups at six locations. *Indicates a significant lower amplitude for BP-I compared to BP-II)

Electrode	Schizophrenia	Bipolar			Controls
		BP-I	BP-II	(difference)	
TCP1	6.84	7.33	8.11	0.78	10.05
TCP2	8.34	8.85	8.96	0.11	11.64
CP1	8.31	9.52	10.54	1.34	12.36
C3	5.86	5.96	6.2	0.24	9.8
F3	2.53	2.47	7.43	4.96*	9.26
P3	11.54	8.51	9.79	1.28	13.5
PZ	12.38	12.69	16.21	3.52*	16.43

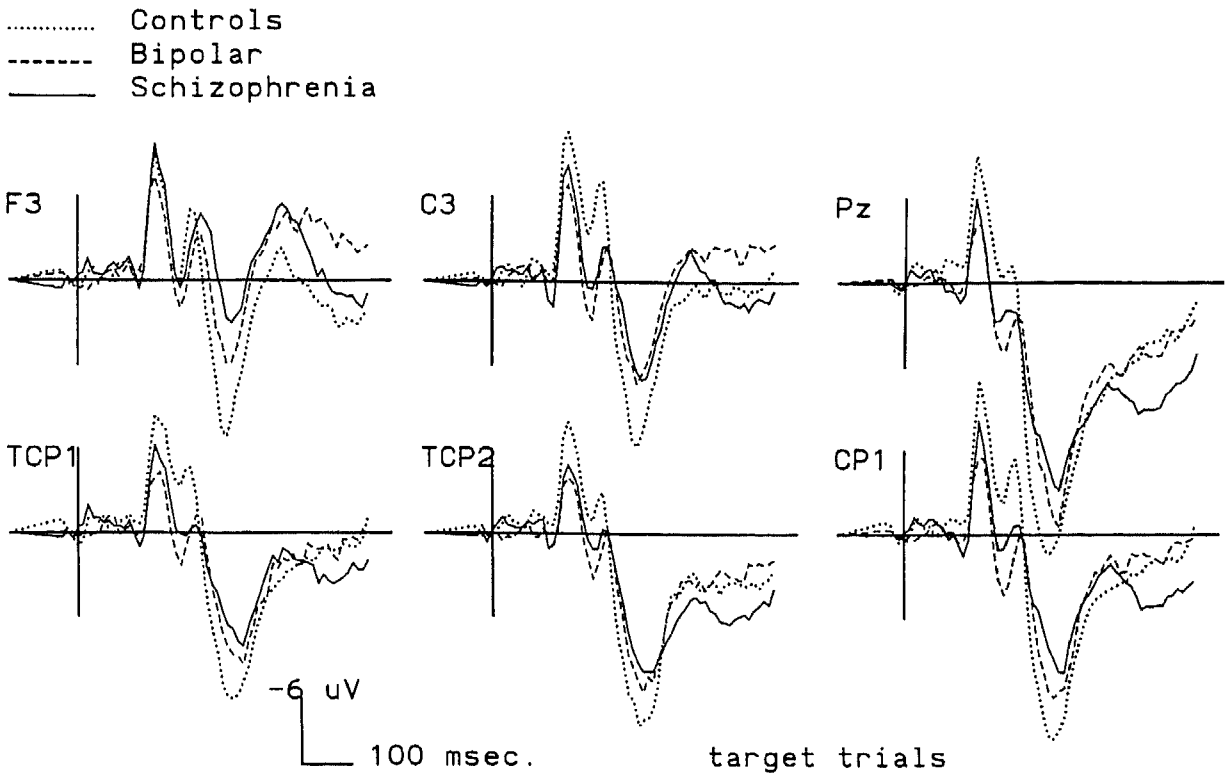

Fig. 2. Mean P300 per group on all six positions showing significant differences between one or more groups.

the following positions: TCP1, TCP2, CP1 and C3. Pairwise group comparisons show a difference between the BD and control group at F3 and P3 electrode sites ($P = 0.03$ and $P = 0.04$, respectively). Further comparison between the BD-I and BD-II groups shows a significant lower amplitude for the BD-I group at the F3 and Pz positions. The mean amplitude for the BD-I group is comparable to that of the schizoprhrenia group at these positions.

Discussion

The lack of finding differences in mean number or localization of white matter lesions between the three groups is remarkable but not unique. In a review Soares and Mann (24) describe this difference as an anatomical key feature that distinguishes BD patients from patients with schizophrenia. However, if one looks closely at the original studies on which the review is based some observations could be made. First, the mean age of both patients and controls is relatively low (mean age 33 years) compared to this study (41.2). Futhermore, the incidence of WML in control groups varies strongly. In studies carried out with comparable methods the range is between 4.3 and 60% (25). From data by Hofman et al. (26) it is clear that the incidence of WML increases rapidly with age both in patient and control groups, and the different findings in our study could therefore be accounted for by the higher mean age of the control group. More specifically, the lack of difference in number of WML between the normal controls and BD patients would be caused by a relatively high number of WML in our control group. Absolute comparisons with previous studies are difficult to make, as the number of subjects per study varies greatly. If one compares the difference between the control group and both patient groups combined (BD + schizophrenia), then the patient groups show more periventricular lesions, the 'Bands' ($P < 0.05$). These findings could point to an accelerated neurodegenerative process in these groups. Compared to normal controls, they would probably encounter WML-related problems earlier in life. Our groups were too small to evaluate this possible relationship.

The ERP data show a different result. From previous research it is known that patients with schizophrenia or unipolar depression have a reduced P300 amplitude (20,27,28). This reduction, which is most pronounced over the left hemi-

sphere, can be regarded as a functional impairment in specific neuronal networks that control the processing of external stimuli (29,30). The group BD patients show a similar topographical impairment in P300 amplitude to schizophrenia patients, with reduced amplitude at left-sided centro-parietal and temporal brain regions. The hypothesis that the BP-I subgroup more resembles the schizophrenia group is supported by these findings. The difference in P300 amplitude in the left frontal brain region (F3) is noteworthy. Together with the gyrus temporalis superior this region plays an important role in the generation of the P300 wave. The finding that activity in this region is specifically impaired in the BD-I group suggests a functional impairment in which frontal brain regions play a major role.

In a study of cognitive functions of these groups (31) BD patients showed the same impaired impaired performance as schizophrenia groups compared to normal controls, despite the fact that testing was carried out during a period of full remission.

Our conclusion from this study is that BD patients suffer from a functional brain disorder that is expressed through a change in physiological response to informative external stimuli and, ultimately, a decline in cognitive functioning. The results of this study suggest that it is possible to distinguish BP-I and BP-II patients on a neurophysiological basis using the P300 paradigm. No neuroanatomical differences between BD-I and BD-II were found, although (frontal) white matter lesions were prominent in both groups. Further studies with larger groups of subject should be conducted to further investigate the functional differences between BD-I and BD-II groups and thus support the distinction made in classification by the DSM-IV.

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